

SMITH (Theo.)

## NOTES

ON A

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HAVING A LOW DEGREE OF VIRULENCE

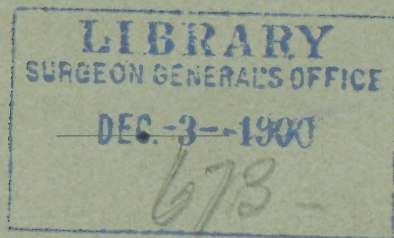
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(From the Laboratory of Comparative Pathology, Harvard  
Medical School)

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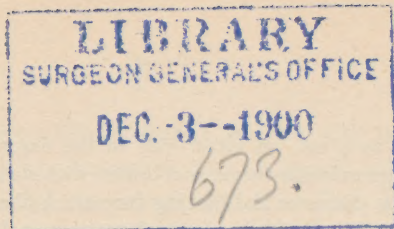
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## NOTES ON A TUBERCLE BACILLUS HAVING A LOW DEGREE OF VIRULENCE.

THEOBALD SMITH, M.D.

*From the Laboratory of Comparative Pathology, Harvard Medical School.*

The tubercle bacillus which is the subject of this communication is the least virulent of the seven human cultures whose pathogenic power I have studied in rabbits and guinea pigs. It does not, however, differ so very much from the rest, and I should not be surprised to find similar bacilli at any time in sputum. The reason for making it the occasion of any special remarks resides in the peculiarity of the case from which it came.

The patient, a man sixty-five years old, was under observation in the Boston City Hospital,<sup>1</sup> which he entered Jan. 25, 1898. In August of last year he noticed a rapidly increasing swelling on the left side of the neck. In a month it had attained the size of an orange. It finally broke and discharged a cupful of "white matter." At the date of his entry into the hospital the swelling had extended to the left side of the face. Below the angle of the jaw were several crater-like openings discharging pus. On February 3 new sinuses had formed. From that date he failed rapidly, and died February 9. I learn that tubercle bacilli in very large numbers were found in the discharge before death. I quote briefly from the autopsy notes (Dr. Mallory):

Body of medium build; considerably emaciated. On the left side of the neck is a large, irregular, ulcerated surface extending from the ear to the larynx. Along the centre is a deep fissure 7 cm. in length, opening into a cavity beneath. The borders of the fissure are very thick, dense, and somewhat nodular. The ulcerated surface in which the fissure lies is irregular,

<sup>1</sup> The clinical history was kindly abstracted for me by Dr. Pearce from the surgical records of the hospital.

extending 2 to 4 cm. on either side of the fissure, is dark red in color, resembling granulation tissue, and dotted with small, yellowish, soft areas 1 to 2 mm. in diameter and looking very much like small abscesses. Just below the ear several cheesy glands about 1 cm. in diameter project through the surface. The skin outside of the ulcerated area is oedematous and light purplish in color. The oedema is most marked in and over the left parotid gland. A second small ulcerated surface 3 cm. in diameter, with central fissure opening into the same cavity beneath the skin, lies lower and further back on the neck just above the outer third of the clavicle. On dissecting back the ulcerative surface the fissure is found to open into a long irregular cavity with dark greenish-colored gangrenous walls extending above to the inner side of the lower ramus of the jaw, below almost to the clavicle, anteriorly almost to the larynx, and posteriorly below to the outer third of the clavicle. Projecting into the cavity is a number of enlarged cheesy, more or less necrotic, lymphatic glands, a few of which are softened and discharging pus. All of the neighboring cervical lymph glands are much enlarged, and on section more or less cheesy in appearance. On the right side of the neck the glands are also much enlarged from just below the ear down to the clavicle. The lowest one is softened and filled with grayish opaque pus. Most of the others show more or less well marked caseation, which in places appears less opaque and more gelatinous than usual. The mass of glands measures 3 to 4 cm. in breadth and 2 cm. in thickness.

Left lung somewhat adherent by old fibrous adhesions. Dependent portions much increased in density; on section, surface gray, granular. On pressure a purulent fluid can be squeezed out, especially from the bronchi and bronchioles. Right lung shows a slight thickening with scarring at the apex, which on section is composed of fibrous tissue with a few small cheesy and calcified areas. Emphysema of both lungs.

Old fibrous adhesions between capsule of liver and diaphragm. Lobules distinct. Just beneath capsule are found scattered over the liver about a dozen small, grayish, transparent areas about 1 mm. in diameter.

*Anatomical Diagnosis.* — Healed tuberculosis of lungs. Acute focal pneumonia. Chronic adhesive pleurisy. Emphysema of lungs. Chronic tuberculosis of lymph glands of the neck with formation of gangrenous cavity and tuberculous ulceration of skin. Slight general arterio-sclerosis. Chronic congestion of spleen and liver. Atrophy of brain. Fatty degeneration of heart. Miliary tuberculosis of liver and spleen.

Cultures from the heart and spleen contained pneumococci and those from the pus of the affected side of neck staphylococci. Those from liver and kidney remained sterile.

The microscopic examination revealed caseation of the lymph glands within the area of disease as well as miliary tubercles and larger tubercular foci in the muscular and connective tissue of the same region. In the liver some old and numerous very small tubercles were detected. In the spleen a few were present.

The source of the culture was a guinea pig which had been inoculated by Dr. Pearce in the abdomen with a bit of tissue from a gland of the affected side. This animal was kindly transferred to me. It was chloroformed after 42 days. In the abdomen the site of the introduced tissue was occupied by a well encapsuled abscess containing very large numbers of tubercle bacilli and cocci of various sizes. Pure cultures of the tubercle bacillus were obtained on dog's serum from both lung and liver foci. Cultures from the abdominal abscesses contained a capsule bacillus and cocci not further examined.

Though the bacilli found in the abdominal abscess in clumps of 10 or more were quite slender and the chromatic substance more or less segmented transversely, the early serum cultures contained quite short rods, like some cultures from sputum. They stained feebly in carbol fuchsin, with the exception of a small percentage of rods which became deeply stained. When the staining was prolonged for 6 to 24 hours all rods became deeply stained, as is the case with most sputum cultures examined. The bacilli multiplied quite rapidly on serum, and produced rich cultures in 2 weeks. The growth differed slightly from former cultures in being more smooth in appearance, less cohesive, and more easily suspended in fluids. There was no difficulty in obtaining rich cultures on glycerine agar from the earliest serum cultures.

The pathogenic power of the pure culture is distinctly below that of the sputum bacilli studied. In comparing various cultures I selected an approximately uniform dose by suspending the bacilli in an indifferent fluid such as normal salt solution or bouillon until the density was nearly that of a bouillon culture of typhoid bacilli 24 hours old, and injected 0.5 cc. of this.<sup>1</sup> The following table gives very briefly the results of tests upon small animals. In order to be fully understood these results should be compared with

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<sup>1</sup> "A Comparative Study of Bovine Tubercle Bacilli and of Human Bacilli from Sputum." "Journ. of Experim. Med.," III. (1898), p. 451.

those given in the article quoted, of which this paper is a continuation.

The most obvious differences between the pathogenic action of this and former cultures are:

1. The prolonged life of the guinea pigs inoculated. In the case of six former cultures the average duration of life following the intra-peritoneal injection of cultures was 17 days. Here it was 41 days for the culture and 67 days for the suspension of bacilli from the peritoneal abscess of the first guinea pig. The subcutaneous injections had likewise a mild effect.

2. The absence of foci in the lungs of the rabbits which received the culture suspensions into an ear vein.

3. The variations in the lesions of the guinea pigs, involving now more or less exclusively the lymph glands, now the liver and spleen. This variation I interpret to indicate an approximate balancing of the pathogenic power and the resistance of the animal.

The supposition that the original glandular lesion might be the result of an inoculation or infection with bovine tubercle bacilli is disproved, because bovine bacilli are 20 to 30 times more virulent. That the bacilli might be avian is made untenable by the result of the inoculation of a pigeon into the pleuro-peritoneal cavity. After 7½ weeks no lesions could be detected. The source of the bacilli can only be conjectured. I am inclined to regard them as disseminated from the lung focus through the blood. Their rapid multiplication in the affected glands of the neck was probably due to the fortuitous assistance of other bacteria accidentally present or subsequently introduced.

In connection with this case it is of interest to note that Arloing and his pupils have been endeavoring to sustain for a number of years the view that the bacilli of the so-called forms of surgical tuberculosis are less virulent than those of the pulmonary disease. There are certain general facts favoring this position. In certain bacterial diseases, either induced experimentally or occurring spontaneously in animals, the more protracted, resisting cases are liable to have

localizations in the skin, subcutis, or the bones. In such cases it is probable that the organs usually most severely involved acquire in the early stages of the disease an increased power of resistance. In guinea pigs, for example, the liver is ordinarily the most severely involved in tuberculosis produced by subcutaneous inoculation. When attenuated cultures or much older animals are used it is the first organ to show reparative changes leading to an irregular cirrhosis and shrinking of the organ. Thus various facts gleaned from comparative etiology support the hypothesis of Arloing that tuberculosis of the lymph glands (scrofula) and bones is due either to bacilli of reduced virulence or else to increased resistance of the individual. This increased resistance may belong to a certain period of life or it may be the result of individual variation.

TABLE OF INOCULATIONS, HUMAN CULTURE VIII.

Designation of animal. (Weight in grams.)	Source of tubercle bacilli.	Mode of inoculation.	RESULT.
Guinea pig from City Hospital.	Bit of tuberculous gland.	abdomen.	Chloroformed after 42 days. Two abscesses in abdomen, containing numerous tubercle bacilli and cocci. Many minute translucent tubercles in lungs. Lesions of liver and spleen slight.
G. p. no. 807 (weight 378).	1 cc. of a dilute suspension of pus from abdominal abscesses of preceding case.	abdomen.	Died in 67 days. Large necroses in liver and spleen. Lymph glands large, but necrosis slight. Testicles embedded in tuberculous tissue. Scattering tubercles in lungs.
G. p. no. 898 (weight 357).	0.5 cc. of a dense suspension of same material as preceding.	subcutis.	Chloroformed in 67 days. Gain in weight 70 grams. Great enlargement of lymph glands, with slight necrosis. Spleen large, with a few necrotic areas. Liver densely sprinkled with irregular grayish foci, but without yellow necroses. Lungs contain a few tubercles only.
G. p. no. 985 (weight 415).	0.5 cc. standard suspension of culture from first g. p., 9 days old; 5th transfer.*	abdomen.	Dies in 41 days. Weight 250. Lymph glands barely affected. Large necrotic areas in liver. Several in spleen. Barely visible translucent tubercles in lungs.
G. p. no. 990 (weight 408).	0.5 cc. same suspension.	subcutis.	Chloroformed after 3 months. Gain in weight 143 grams. Local ulcer now inconspicuous. Spleen small. Malpighian bodies somewhat conspicuous. Liver shows a few depressed scar-like lines. Lungs free. Bronchial glands enlarged, without necroses. Invasion of lymph glands from point of inoculation as far as retro-peritoneal (lumbar) gland of same side.
Rabbit no. 31 (weight 1,570).	0.5 cc. same suspension.	ear vein.	Chloroformed after 3 mos. and 6 days. Gained 170 grams. In each kidney 2 linear radial disintegrated foci containing tubercle bacilli. No other lesions.
Rabbit no. 23 (weight 2,230).	1.5 cc. same suspension.	ear vein.	Chloroformed after 3 mos. and 6 days. Lost 176 grams. Numerous elongated radial foci in both kidneys. No other lesions.
Pigeon no. 9.	1.4 cc. pus suspension. (See above.)	pleuro-peritoneal cavity.	Chloroformed after 53 days. No lesions.

\* Total period of artificial cultivation, 3 months less 2 days.







